DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-228/S-002

Pharmacia & Upjohn
Attention: Gregory G. Shawaryn
Regulatory Manager Regulatory Affairs
7000 Portage Road
Kalamzoo, MI 49001

21 SEP 2001

Dear Mr. Shawaryn:

Please refer to your supplemental new drug application dated July 6, 2001, received July 6, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Detrol® LA (tolterodine tartrate) extended release capsules.

This "Changes Being Effected" supplemental new drug application provides for the following revisions to the **DESCRIPTION, CLINICAL PHARMACOLOGY, CLINICAL STUDIES, PRECAUTIONS** and **ADVERSE EVENTS** sections in the package insert:

DESCRIPTION section:
Deletion of the phrase "ammonium hydroxide" in the third paragraph in this section, to read as follows:

> DETROL LA for oral administration contains 2 mg or 4 mg of tolterodine tartrate. Inactive ingredients are sucrose, starch, hydroxypropyl methylcellulose, ethylcellulose, medium chain triglycerides, oleic acid, gelatin, and FD&C Blue #2. The 2 mg capsules also contain yellow iron oxide. Both capsule strengths are imprinted with a pharmaceutical grade printing ink that contains shellac glaze, titanium dioxide, propylene glycol, and simethicone.

CLINICAL PHARMACOLOGY section:
Editorial change in the **Other Drugs Metabolized by Cytochrome P450 Isoenzymes** subsection, to read as follows:

> In vivo drug-interaction data show that tolterodine immediate release does not result in clinically relevant inhibition of CYP1A2, 2D6, 2C9, 2C19,or 3A4 as evidenced by lack of influence on the marker drugs caffeine, debrisoquine, S-warfarin, and omeprazole.

CLINICAL STUDIES section:
Editorial change in Table 2 header, to read as follows:

Table 2. 95% Confidence Intervals (CI) for the Difference between DETROL LA (4 mg daily) and Placebo for Mean Change at Week 12 from Baseline*

PRECAUTIONS section:
Addition of two additional adverse events in the **Information for Patient** subsection, to read as follows:

> Patients should be informed that antimuscarinic agents such as Detrol LA may produce the following effect: blurred vision, dizziness, or drowsiness.

Editorial correction to delete the phrase "cause embryolethality" and replace with "be embryolethal" in the second sentence of the **Pregnancy** subsection, to read as follows:

> When given at doses of 30 to 40 mg/kg/day, tolterodine has been shown to be embryolethal and reduce fetal weight, and increase the incidence of fetal abnormalities (cleft palate, digital abnormalities, intra-abdominal hemorrhage, and various skeletal abnormalities, primarily reduced ossification) in mice.

ADVERSE EVENTS section:
Addition of a **Postmarketing Surveillance** subsection under the **ADVERSE REACTIONS** section, to read as follows:

> **Postmarketing Surveillance**
> The following events have been reported in association with tolterodine use in clinical practice: anaphylactoid reactions, tachycardia, and peripheral edema. Because these spontaneously reported events are from the worldwide postmarketing experience, the frequency of events and the role of tolterodine in their causation cannot be reliably determined.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted July 6, 2001).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-228/S-002." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

> MEDWATCH, HF-2
> FDA
> 5600 Fishers Lane
> Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Susan Allen, M.D., M.P.H.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research